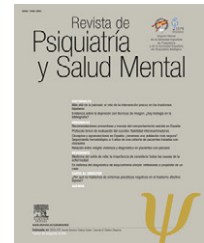




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## EDITORIAL

### Imaging evidence for depression: Is there biology in the bibliography?☆

### Evidencia sobre la depresión con técnicas de imagen: ¿hay biología en la bibliografía?

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#### Introduction

Medical imaging has undoubtedly had a profound influence on clinical practice. Although this technology has been successfully translated to imaging the brain—*neuroimaging*—there has been disappointingly little impact on the management of individual patients presenting at psychiatry clinics. Neuroimaging, or to be more precise its interpretation, has been derided as merely a new phrenology, but it remains a central pillar of an evolving evidence base putting psychiatry on a convergent course with other disciplines, as medical practice becomes medical science.

Major depressive disorder (MDD) is the fourth leading cause of disease burden worldwide, and is associated with chronic physical illnesses placing it to become second only to heart disease in terms of disease burden.<sup>1</sup> The aetiology of MDD is far from a complete understanding, although it might be hoped that its biological loci could be described with some precision by the wide range of structural and functional imaging techniques at our disposal. The physical principles that underpin these techniques and the corresponding measurements they make are varied and distinct. What unites them is that when distinguishing pathological changes in anatomy and physiology, the observed effect sizes are small. Consequently, even for such a prevalent disorder, the prospects for imaging as a diagnostic or prognostic test look unlikely in the foreseeable future.

Notwithstanding this gloomy analysis, much has been learnt about the neurobiological basis of MDD from imaging and other techniques. Indeed, it is now clear from these direct observations that there is a neurobiological basis for the disorder favouring the unitarian model codified in DSM-III. Much of the convincing evidence for this has come the synthesis of published work as meta-analyses, a technique recently reframed for imaging studies.<sup>2</sup> However, whether the brain differences associated with MDD represent a cogent model requires careful examination. Here we see if pieces really do fall into place.

#### The hypothalamus–pituitary–adrenal axis

HPA axis hyperactivity, leading to prolonged hypercortisolemia is a potentially powerful model of MDD that predicts cellular changes of brain areas that have a high concentration of glucocorticoid receptors such as the hippocampus, amygdala and cingulate cortex; areas of the limbic system involved in mood regulation.

The mainstay of studies of the HPA axis has been structural MRI using manual tracing of regions with hypothesised involvement. Perhaps surprisingly, the eponymous regions of the model have been the least-well studied, with a recent attempt at a meta-analysis being described as “futile”.<sup>3</sup> In contrast, meta-analyses have confirmed a highly significant reduction in the volume of the hippocampus and anterior cingulate associated with MDD<sup>4</sup> that is not replicated in combined volume measurements of the amygdala.<sup>4–6</sup> The hippocampus is also sensitive to prolonged illness, with longer durations associated with smaller volumes.<sup>7</sup> At the cellular level, neurogenesis in the hippocampus mediated by selective serotonin reuptake inhibitor

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(SSRI) treatment<sup>8,9</sup> has been shown to arise through accelerated maturation of immature granule cells.<sup>10</sup> However, observing the predictions of these animal model data of increased hippocampal volumes in medicated patients is restricted by the small quantity of source data, although greater volume loss with moderate rather than severe duration of illness may indicate a restorative effect by chronic treatment.<sup>7</sup>

The amygdala has a similarly uneven (although distinct) pattern of volume change. Several meta-analyses have failed to find overall differences<sup>4–6</sup> and no relationship has been found with chronicity.<sup>5</sup> However, stratifying according to medication status reveals a decrease in amygdala volume in drug naive patients. Conversely, treated patients have an increase in volume paralleling increased activity that accompanies acute administration of SSRI in a dose-responsive manner.<sup>11</sup> Furthermore, chronicity is strongly confounded with medication history, potentially masking its effect.

The overall picture therefore is of differential sensitivities of the components of the HPA axis to hypercortisolemia induced by depressive episodes. It is interesting to note that when studies looking at the entire cortex (rather than just a few regions) are combined, the only area that significantly characterises MDD is the anterior cingulate,<sup>12</sup> suggesting small effects and/or variable results across studies. The down-regulation activity by SSRI treatment<sup>13</sup> has analogous heterogeneity across the HPA axis. Whether volume reductions predate clinical symptoms remains unknown. Meta-analysis of children with MDD provides no evidence either way,<sup>7</sup> although an article published subsequently<sup>14</sup> found that morphologic changes might be evident initially and that genetic differences may increase vulnerability to early-life stress, and thus the risk of MDD.

### The fronto-limbic model

A simple but influential systems-level model for depression is that enhanced “bottom-up” limbic activation by negative stimuli, in the absence of effective “top-down” inhibitory control by prefrontal cortex, may predispose to ruminative amplification of negatively valenced events, attentional bias to negative stimuli, and reduced capacity to reconstruct negative cognitions, leading to the emergence of depressive symptoms.<sup>15</sup> This cognitive model predicts over-activation of the (para)limbic system (particularly amygdala and anterior cingulate cortex) by negative emotional stimuli in conjunction with under-activation of prefrontal cortical areas that are reciprocally connected to limbic structures and are thought to play an important role in mood regulation.

Meta-analyses of cross-sectional functional MRI studies of patients with MDD generally support the predicted patterns of increased limbic and decrease prefrontal activity. However, there is limited overlap of significant effects between studies.<sup>16,17</sup> It would be easy to dismiss this as a result of differences in methodologies, however a lack of consistency in the location of activation may in fact be a marker of MDD.<sup>17</sup> Effective pharmacotherapy with SSRI is associated with “normalization” of initial over-activation of limbic regions and the opposite trend, toward increased activation

following treatment, in regions of prefrontal and cingulate cortex.<sup>18</sup>

An observation arising from the meta-analyses is the emergence of other regions outside of the fronto-limbic system with reduced activation in patients.<sup>16</sup> Whilst interesting, this is not unexpected given that most studies are explorative and thus report effects from across the entire cortex. These additional regions include the posterior cingulate and other components of the so-called default mode network, frequently linked to self-monitoring.<sup>19</sup> Abnormal activation in these regions can easily be envisaged as playing a key role in ruminative behavior. Meta analyses of resting cerebral blood flow with positron emission tomography has also demonstrated the sensitivity of these regions to SSRI treatment.<sup>16</sup>

In this brief overview of the current evidence for a neurobiology substrate to MDD we have necessarily had to narrow our focus to just two models. Summarizing the findings takes us in two apparently contradictory routes. On the one hand, there is good support for the consistent involvement of HPA axis and fronto-limbic brain systems in MDD; a significant achievement compared to our knowledge only a decade ago. On the other hand, there are clearly additional complexities in the data that are not adequately accounted for by the existing models as they are described. In short, it looks unlikely that a reductionist approach will lead to a sufficient or useful description of MDD. Indeed, this is the case more generally across the inventory of mental health disorders. Compartmental models in which areas are imbued with specific functions and sensitivities do not acknowledge the distributed and integrative nature of the brain function. As the techniques to measure the brain mature, an evolution is also needed in our conceptualization of its organization, function and dysfunction.

### Conflict of interest

The author has no conflict of interest to declare.

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